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## HIV Care & PMTCT in Resource-Limited Settings

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prepared by the Bordeaux Working Group

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Becquet R, Leroy V. **The challenges of preventing mother-to-child transmission of HIV in Africa**. *Presse Medicale* 2007;36 (12) Part 3:1947-1957.

**Abstr.** HIV (human immunodeficiency virus) is the leading cause of infant mortality in Africa where 1700 children are infected each day principally by mother-to-child transmission. Prevention of this risk is therefore a public health priority. Considerable progress has been made in the past 10 years in preventing the risk of mother-to-child transmission in the peripartum period in Africa: short antiretroviral regimens during the third trimester of pregnancy can reduce transmission rates to less than 5%. Breast-feeding, which is widespread and prolonged in Africa, causes many HIV infections and thus reduces the efficacy of peripartum interventions. Interventions that offer alternatives to prolonged breast-feeding and are both socially acceptable and safe for the infant can effectively reduce the risk of postnatal HIV transmission. But operational implementation of these postnatal interventions remains complex. Use of antiretroviral agents as prophylaxis for mother and child during the breast-feeding period and clinical management of breast-feeding mothers with combined antiretroviral treatments offer hope that the risk of postnatal HIV transmission can be reduced but the effectiveness and safety of these interventions still need to be assessed.

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Chiappini E, Galli L, Gabiano C, Gattinara GC, Martino A, Scolfaro C, de Martino M. **Preventable zidovudine overdose during postnatal prophylaxis in healthy children born to HIV-1-positive mothers** [Correspondance]. *AIDS* 2008;22(2):316-7.

Coffie PA, Ekouevi DK, Chaix ML, Tonwe-Gold B, Clarisse AB, Becquet R, Viho I, N'Dri-Yoman T, Leroy V, Abrams EJ, Rouzioux C, Dabis F. **Maternal 12-month response to antiretroviral therapy following prevention of mother-to-child transmission of HIV type 1, Ivory Coast, 2003-2006**. *Clinical Infectious Diseases* 2008;46(4):611-21.

**Abstr.** OBJECTIVE: Our aim was to study the response to antiretroviral treatment among women exposed to single-dose nevirapine (NVP) and/or short-course zidovudine (ZDV; with or without lamivudine [3TC]) for the prevention of mother-to-child transmission of human immunodeficiency virus (HIV) infection. METHODS: All HIV type 1-infected women who initiated antiretroviral treatment with stavudine or ZDV, 3TC, and NVP or efavirenz were eligible for the MTCT-Plus program in Abidjan, Ivory Coast. Exposed women had received either single-dose NVP alone or short-course ZDV (with or without 3TC) plus single-dose NVP during previous pregnancy. Genotypic resistance testing was performed at week 4 after delivery. Virologic failure was defined as a plasma HIV RNA level >500 copies/mL 12 months after initiation of antiretroviral treatment. RESULTS: Among 247 women who received antiretroviral treatment, 109 (44%) were unexposed; 81 had received short-course ZDV with 3TC, as well as single-dose NVP; 5 had received short-course ZDV plus 3TC; 50 had received short-course ZDV plus single-dose NVP; and 2 had received single-dose NVP alone. No ZDV mutation was detected in the 115 women whose specimens were available for genotypic testing; 11 (15.1%) of 73 women with 3TC exposure who were tested after delivery had 3TC resistance mutations. Three (4.3%) of 69 women exposed to short-course ZDV and 3TC plus single-dose NVP and 16 (38.1%) of 42 women exposed to short-course ZDV plus single-dose NVP had NVP resistance mutations. Antiretroviral treatment was initiated a median of 21 months after the intervention to prevent mother-to-child HIV transmission (median CD4(+) T lymphocyte count, 188 cells/mm<sup>3</sup>). Month 12 virologic failure was identified in 42 (19.2%) of 219 women for whom data were available, and multivariate analysis revealed that it was associated with poor adherence to treatment (adjusted odds ratio [aOR], 12.7; 95% confidence interval [CI], 3.0-53.9), postpartum 3TC resistance mutations (aOR, 6.9; 95% CI, 1.1-42.9), and a baseline CD4(+) T lymphocyte count <200 cells/mm<sup>3</sup> (aOR, 0.3; 95% CI, 0.2-0.8). NVP resistance was not associated with virological failure (aOR, 1.8; 95% CI, 0.5-6.5). CONCLUSIONS: Our study found that

poor adherence and 3TC resistance acquired after the intervention to prevent mother-to-child transmission of HIV infection were associated with virologic failure in women who initiated antiretroviral treatment.

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Cohen K, van Cutsem G, Boulle A, McIlleron H, Goemaere E, Smith PJ, Maartens G. **Effect of rifampicin-based antitubercular therapy on nevirapine plasma concentrations in South African adults with HIV-associated tuberculosis.** Journal of Antimicrobial Chemotherapy 2008;61(2):389-93.

**Abstr.** BACKGROUND AND OBJECTIVES: Nevirapine-containing antiretroviral therapy (ART) and rifampicin-based antitubercular therapy are commonly co-administered in Africa, where nevirapine is often the only available non-nucleoside reverse transcriptase inhibitor. Rifampicin induces the metabolism of nevirapine, but the extent of the reduction in nevirapine concentrations has varied widely in previous studies. We describe the steady-state pharmacokinetics of nevirapine during and after antitubercular therapy in South African patients. METHODS: Sixteen patients receiving ART including standard doses of nevirapine were admitted twice for intensive pharmacokinetic sampling: during and after rifampicin-based antitubercular therapy. RESULTS: Geometric mean ratios for nevirapine pharmacokinetic parameters during versus after antitubercular therapy were 0.61 [90% confidence interval (CI) 0.49-0.79] for C<sub>max</sub>, 0.64 (90% CI 0.52-0.80) for area under the curve up to 12 h (AUC(0-12)) and 0.68 (90% CI 0.53-0.86) for C<sub>min</sub>. Nevirapine C<sub>min</sub> was subtherapeutic (<3 mg/L) in six patients during antitubercular therapy (one of whom developed virological failure) and in none afterwards. There was no correlation between rifampicin concentrations and the degree of nevirapine induction assessed by the proportional change in nevirapine concentrations between the two admissions. The ratio of nevirapine AUC(0-12) to the AUC(0-12) of its 12-hydroxy metabolite was significantly lower in the presence of antitubercular therapy, consistent with induced metabolism. CONCLUSIONS: Nevirapine concentrations were significantly decreased by concomitant rifampicin-based antitubercular therapy and a high proportion of patients had subtherapeutic plasma concentrations. Further study in African patients is required to determine the implications for treatment outcomes.

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Ekouevi DK, Inwoley A, Tonwe Gold B, Danel C, Becquet R, Viho I, Rouet F, Dabis F, Anglaret X, Leroy V. **Variation of CD4 count and percentage during pregnancy and after delivery: Implications for HAART initiation in resource-limited settings.** AIDS Research and Human Retroviruses 2007;23(12):1469-1473.

**Abstr.** We studied whether the use of T-lymphocyte CD4(+) (CD4) absolute count instead of CD4 percentage could affect the decision process regarding HAART initiation in African HIV-infected pregnant women. A prospective cohort in Abidjan, Cote d'Ivoire before HAART was available. Participating women received a perinatal antiretroviral prophylaxis (zidovudine + single-dose of nevirapine). CD4 count and percentage were measured by flow cytometry at baseline (32 weeks of amenorrhea) and at 1 month after delivery. A signed-rank test was used to compare the distributions of the CD4 absolute count and percentage values. A total of 325 HIV-1-infected pregnant women were included. At baseline, their median CD4 count was 355 cells/mm<sup>3</sup> and the median CD4 percentage was 24.8%; 17.8% of women had a CD4 count < 200 cells/mm<sup>3</sup> and 14.8% had a CD4 percentage < 15%. One month after delivery, the median CD4 count was 489 cells/mm<sup>3</sup> (vs. baseline: p < 0.001), the median CD4 percentage was 25.6% (vs. baseline: p = 0.107), 9.5% of women had CD4 count < 200 cells/mm<sup>3</sup> (vs. baseline: p < 0.001), and 15.1% of women had a CD4 percentage < 15% (vs. baseline: p = 0.823). When combining the CD4 count and the WHO clinical stage, the proportion of women who met the WHO 2006 criteria for initiating HAART was 28.3% at baseline but

17.2% only at 1 month after delivery ( $p < 0.001$ ). Between the prepregnancy and the postdelivery periods, the CD4 count experienced a significant increase, whereas the CD4 percentage remained unchanged. To accurately target the most appropriate time to start HAART, the CD4 percentage could be more reliable than the absolute count in sub-Saharan African pregnant women.

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Fairall LR, Bachmann MO, Louwagie GMC, van Vuuren C, Chikobvu P, Steyn D, Staniland GH, Timmerman V, Msimanga M, Seebregts CJ, Boule A, Nhwatiwa R, Bateman ED, Zwarenstein MF, Chapman RD. **Effectiveness of antiretroviral treatment in a South African program - A cohort study**. Archives of Internal Medicine 2008;168(1):86-93.

**Abstr.** Background: The effectiveness of the South African government's expanding antiretroviral treatment program is unknown. Observational studies of treatment effectiveness are prone to selection bias, rarely compare patients receiving antiretroviral treatment with similar patients not receiving antiretroviral treatment, and underestimate mortality rates unless patients are actively followed up. Methods: We followed up 14 267 patients in the Public Sector Anti-Retroviral Treatment project in Free State, South Africa, for up to 20 months after enrollment. A total of 3619 patients received highly active triple antiretroviral treatment (HAART) for up to 19 months (median, 6 months; interquartile range, 3-9 months) after enrollment. Patients' clinical data were linked with the national mortality register. Marginal structural regression models adjusted for baseline and time-varying covariates. Results: Of 4570 patients followed up for at least 1 year, 53.2% died. Eighty-seven percent of patients who died had not received HAART. HAART was associated with lower mortality (hazard ratio, 0.14; 95% confidence interval [CI], 0.11-0.18) and with the presence of tuberculosis (hazard ratio, 0.61; 95% CI, 0.46-0.81) after adjusting for age, sex, weight, clinic, district, CD4 cell count, cotrimoxazole therapy, tuberculosis at baseline, and previous antiretroviral therapy. Cotrimoxazole therapy was associated with lower mortality (hazard ratio, 0.37; 95% CI, 0.32-0.42). Each month of HAART was associated with an increase in CD4 cell count of 15.1 cells/ $\mu$ L (95% CI, 14.7-15.5 cells/ $\mu$ L) and with an increase in body weight of 602.9 (95% CI, 548-658 g). Conclusions: HAART provided through these South African government health services seems as effective as that provided in high-income countries. Delays starting HAART contributed to high mortality rates. Faster expansion and timely commencement of HAART are needed.

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Gray GE. **Walking the tightrope in prevention of mother-to-child transmission of HIV infection [Editorial]**. Clinical Infectious Diseases 2008;46(4):622-624.

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Jaen A, Esteve A, Miro JM, Tural C, Montoliu A, Ferrer E, Riera M, Segura F, Force L, Sued O, Vilaro J, Garcia I, Masabeu A, Altes J, Coltet B, Podzamczar D, Murillas J, Navarro G, Gatell JM, Casabona J. **Determinants of HIV progression and assessment of the optimal time to initiate highly active antiretroviral therapy: PISCIS Cohort (Spain)**. Journal of Acquired Immune Deficiency Syndromes 2008;47(2):212-20.

**Abstr.** OBJECTIVE: We analyze the factors related to progression to AIDS or death in HIV-infected patients from the Proyecto para la Informatizacion del Seguimiento Clinico epidemiologico de los pacientes con Infeccion por VIH/SIDA (PISCIS) Cohort and we assess the optimal time to initiate highly active antiretroviral therapy (HAART) taking lead time into account. METHODS: We selected naive patients who were AIDS-free and initiated HAART after January 1998. Statistical analyses were performed using Cox

proportional hazards models. Lead time was defined as the time it took the deferred group with an early disease stage to reach the later stage. The analysis accounting for lead time was performed using multiple imputation methods based on estimates from the pre-HAART period as described elsewhere. RESULTS: Multivariate analysis on 2035 patients (median follow-up = 34.3 months) showed significantly higher hazard ratios (HRs) for a CD4 count <200 cells/microL (HR = 3.79, 95% confidence interval [CI]: 2.18 to 6.57), HIV-1 RNA level >100,000 copies/mL (HR = 1.84, 95% CI: 1.26 to 2.69), and hepatitis C virus (HCV) coinfection (HR = 2.40, 95% CI: 1.65 to 3.49), whereas a lower risk was found for those who started HAART between January 2001 and June 2004 (HR = 0.55, 95% CI: 0.30 to 0.90). When lead time and unseen events were included, we found a higher risk of progression to AIDS among patients who deferred treatment when the CD4 count reached <200 cells/microL (HR = 2.97, 95% CI: 1.91 to 4.63) and 200 to 350 cells/microL (HR = 1.85, 95% CI: 1.03 to 3.33) compared with those who started treatment with CD4 counts from 200 to 350 cells/microL and >350 cells/microL, respectively. CONCLUSIONS: Advanced HIV disease, HCV coinfection, and early HAART period were determinants of AIDS progression or death. Lead-time analysis in asymptomatic HIV-infected patients suggests that the best time to start HAART is before the CD4 count falls to lower than 350 cells/microL.

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Knobel H, Guelar A, Montero M, Carmona A, Luque S, Berenguer N, Gonzalez A. **Risk of side effects associated with the use of nevirapine in treatment-naive patients, with respect to gender and CD4 cell count.** HIV Medicine 2008;9(1):14-8.

**Abstr.** OBJECTIVES: A warning about the use of nevirapine (NVP) by its pharmaceutical manufacturer has been issued in which it has been recommended that NVP should not be prescribed in patients with increased risk of toxicity based on CD4 cut-offs and gender. The aim of this study was to determine whether these recommendations are of use in preventing side effects. METHODS: This retrospective study included antiretroviral drug-naive patients who started treatment with NVP. Patients were divided into two groups: those with high CD4 counts (H; women: CD4 count >250 cells/microL; men: CD4 count >400 cells/microL) and those with low CD4 counts (L; women: CD4 count <250 cells/microL; men: CD4 count <400 cells/microL). RESULTS: A total of 142 patients were included in the study, 61 in the H group and 81 in the L group. Skin rash developed in 6.56% of patients [95% confidence interval (CI) 2.67-15.70%] in the H group and in 14.81% of patients (95% CI 8.72-24.17%) in the L group (P=0.18). Hepatotoxicity developed in 4.92% (95% CI 1.79-13.50%) and 6.17% (95% CI 2.73-13.66%) of patients with high and low CD4 cell counts, respectively (P=1.0). CONCLUSION: The recommendations not to use NVP in drug-naive patients at increased risk of toxicity on the basis of gender and CD4 cell count do not seem to be of use in preventing the occurrence of side effects. However, a small number of patients were included in this study, and hence the possibility cannot be excluded that the recommendations are appropriate in another clinical practice setting.

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Patel K, Hernan MA, Williams PL, Seeger JD, McIntosh K, Van Dyke RB, Seage GR. **Long-term effectiveness of highly active Antiretroviral therapy on the survival of children and adolescents with HIV infection: A 10-year follow-up study.** Clinical Infectious Diseases 2008;46(4):507-515.

**Abstr.** Background. Previous observational studies found highly active antiretroviral therapy (HAART) to be associated with improved survival among human immunodeficiency virus (HIV)-infected children and adolescents. However, these studies had limited follow-up of HIV-infected children undergoing HAART. Given that HIV infection is chronic and that exposure to HAART is likely to be life-long, there is a need to

evaluate the long-term effect of HAART on survival in this population. **Methods.** The study included 1236 children and adolescents who were perinatally infected with HIV, who were on study or enrolled after January 1996 in a United States-based multicenter prospective cohort study (Pediatric AIDS Clinical Trials Group 219/219C), and who were not receiving HAART at baseline; subjects were observed for a maximum of 10 years through June 2006. A weighted Cox regression model was used to estimate the effect of HAART on survival, appropriately adjusted for time-varying confounding by severity. **Results.** At the end of the 10-year follow-up period (median duration of follow-up, 6.3 years; interquartile range, 4.3-9.8 years), 70% of participants had initiated HAART. Lower CD4 cell percentages, total lymphocyte counts, and albumin levels were associated with an increased probability of initiating HAART. Eighty-five deaths were observed, and the mortality hazard ratio associated with HAART, compared with non-HAART regimens, was 0.24 after adjusting for measured confounding by severity (95% confidence interval, 0.11-0.51). **Conclusions.** The use of HAART was highly effective in reducing mortality during the period 1996-2006 among children and adolescents infected with HIV. With improved long-term survival, continued follow-up is necessary to evaluate the effects of prolonged use of HAART on potential adverse events, immune function, growth, sexual maturation, and quality of life in this population.

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Rouet F, Chaix ML, Inwoley A, Anaky MF, Fassinou P, Kpozehouen A, Rouzioux C, Blanche S, Msellati P. **Frequent occurrence of chronic hepatitis B virus infection among West African HIV type-1-infected children.** *Clinical Infectious Diseases* 2008;46(3):361-6.

**Abstr.** **BACKGROUND:** The aim of this study, conducted in Ivory Coast, was to evaluate the prevalence and evolution of viral hepatitis in children coinfecting with human immunodeficiency virus type 1 (HIV-1). **METHODS:** Hepatitis B virus (HBV) and hepatitis C virus (HCV) markers were retrospectively and longitudinally assessed among 280 HIV-1-infected children enrolled in the Agence Nationale de Recherches sur le SIDA et les Hepatites Virales B et C 1244/1278 cohort. Among these, 173 (61.8%) received highly active antiretroviral therapy (HAART), including lamivudine (3TC) for 122 children. Detection of the hepatitis B s antigen (HBsAg) was performed on specimens collected at inclusion and 6 months later. If results of both tests were positive, hepatitis B e antigen (HBeAg)/hepatitis B e antibody (HBeAb) and HBV DNA levels were measured at inclusion and during follow-up. A fourth-generation HCV enzyme immunoassay was used for HCV screening at inclusion. **RESULTS:** In our pediatric cohort, no patients were infected with HCV, but the prevalence of HBsAg at inclusion was 12.1% (34 of 280; 95% confidence interval [CI], 8.6-16.6). Among the HBV-HIV-1-coinfecting children, a high rate of positive HBeAg chronic hepatitis B (CHB) was noted at inclusion (82.4% [28 of 34]; 95% CI, 65.5%-93.2%) and after a median follow-up of 18 months (78.3%; 95% CI, 45.5%-92.7%), with no significant difference between children treated with HAART (with or without 3TC) and untreated ones. These children showed high HBV DNA levels (usually >8.0 log<sub>10</sub> copies/mL) and viral population consisting of nearly exclusively wild-type HBeAg-positive HBV strains, strongly suggesting that most of them were in the initial immunotolerant phase of chronic hepatitis B. **CONCLUSION:** In sub-Saharan Africa, children with chronic hepatitis B and who are treated with 3TC-based HAART are at risk of developing 3TC resistance. Further studies are required to guide the management of HBV-HIV-1-coinfecting children.

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Sinha G, Dyalchand A, Khale M, Kulkarni G, Vasudevan S, Bollinger RC. **Low utilization of HIV testing during pregnancy - What are the barriers to HIV testing for women in rural India?** Journal of Acquired Immune Deficiency Syndromes 2008;47(2):248-252.

**Abstr.** Introduction: Sixty percent of India's HIV cases occur in rural residents. Despite government policy to expand antenatal HIV screening and prevention of maternal-to-child transmission (PMTCT), little is known about HIV testing among rural women during pregnancy. Methods: Between January and March 2006, a cross-sectional sample of 400 recently pregnant women from rural Maharashtra was administered a questionnaire regarding HIV awareness, risk, and history of antenatal HIV testing. Results: Thirteen women (3.3%) reported receiving antenatal HIV testing. Neither antenatal care utilization nor history of sexually transmitted infection (STI) symptoms influenced odds of receiving HIV testing. Women who did not receive HIV testing, compared with women who did, were 95% less likely to have received antenatal HIV counseling (odds ratio = 0.05, 95% confidence interval: 0.02 to 0.17) and 80% less aware of an existing HIV testing facility (odds ratio 0.19, 95% confidence interval: 0.04 to 0.75). Conclusions: Despite measurable HIV prevalence, high antenatal care utilization, and STI symptom history, recently pregnant rural Indian women report low HIV testing. Barriers to HIV testing during pregnancy include lack of discussion by antenatal care providers and lack of awareness of existing testing services. Provider-initiated HIV counseling and testing during pregnancy would optimize HIV prevention for women throughout rural India.

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Stringer EM, Chia BH, Chintua N, Creek TL, Ekouevi DK, Coetzee D, Tih P, Boulle A, Dabis F, Shaffer N, Wilfert CM, Stringer JS. **Monitoring effectiveness of programmes to prevent mother-to-child HIV transmission in lower-income countries.** Bulletin of the World Health Organization 2008;86(1):57-62.

**Abstr.** Ambitious goals for paediatric AIDS control have been set by various international bodies, including a 50% reduction in new paediatric infections by 2010. While these goals are clearly appropriate in their scope, the lack of clarity and consensus around how to monitor the effectiveness of programmes to prevent mother-to-child HIV transmission (PMTCT) makes it difficult for policy-makers to mount a coordinated response. In this paper, we develop the case for using population HIV-free child survival as a gold standard metric to measure the effectiveness of PMTCT programmes, and go on to consider multiple study designs and source populations. Finally, we propose a novel community survey-based approach that could be implemented widely throughout the developing world with minor modifications to ongoing Demographic and Health Surveys.

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**Free Full Text:** <http://www.scielosp.org/pdf/bwho/v86n1/16.pdf>

Walker AS for the *DART Trial Team*. **Fixed duration interruptions are inferior to continuous treatment in African adults starting therapy with CD4 cell counts < 200 cells/ $\mu$ l.** AIDS 2008;22(2):237-247.

**Abstr.** Background: Structured treatment interruption (STI) of antiretroviral therapy (ART) could potentially reduce cost and toxicity, but clinical efficacy requires evaluation. Methods: An assessment of fixed-duration STI was nested in DART, a multicentre trial comparing strategies for monitoring ART in Uganda and Zimbabwe (ISCRTN 13968779). Of 3316 ART-naive symptomatic adults with CD4 cell count < 200 cells/ $\mu$ l at ART initiation, 813 with  $\geq$  300 cells/ $\mu$ l after 48 or 72 weeks underwent a second randomization to either STI, cycles of 12 weeks on/off (408), or continuous ART (CT; 405). Results: Median age at STI/CT randomization was 37 years (range, 19-67) and CD4 cell count 358 cells/ $\mu$ l (range, 300-1054). A second review terminated the STI/CT randomisation on 15 March 2006, and participants changed to CT. Median follow-up was

51 weeks (range, 0-85): 99% and 50% of time was spent on ART in CT and STI, respectively. First new World Health Organization (WHO) stage 4 events or death occurred more frequently in STI (24; 6.4/100 person-years) than CT (9; 2.4/100 person-years) (hazard ratio, 2.73; 95% confidence interval, 1.27-5.88; P=0.007); oesophageal candidiasis being the most frequent event (STI, 13; CT, 3). Nine (1%) participants died (STI, 5; CT, 4). There was no difference in time to first serious adverse event (P=0.78), although ART change owing to toxicity occurred more with CT (10; 2.6/100 person-years) than with STI (2; 0.5/100 person-years) (P=0.02). Conclusions: Although absolute rates of WHO stage 4 events/death were low, 12 week STIS initiated at a CD4 cell count  $\geq$  300 cells/ $\mu$ l resulted in a greater than twofold increased relative rate of disease progression compared with continuous therapy in adult Africans initiating ART with advanced disease, and cannot be recommended. .

Warszawski J, Tubiana R, Le Chenadec J, Blanche S, Teglas JP, Dollfus C, Faye A, Burgard M, Rouzioux C, Mandelbrot L. **Mother-to-child HIV transmission despite antiretroviral therapy in the ANRS french perinatal cohort.** AIDS 2008;22(2):289-299.

**Abstr.** Objective: To identify factors associated with mother-to-child HIV-1 transmission (MTCT) from mothers receiving antenatal antiretroviral therapy. Design: The French Perinatal Cohort (EPF), a multicenter prospective cohort of HIV-infected pregnant women and their children. Methods: Univariate analysis and logistic regression, with child HIV status as dependent variable, were conducted among 5271 mothers who received antiretroviral therapy during pregnancy, delivered between 1997 and 2004 and did not breastfeed. Results: The MTCT rate was 1.3% [67/5271; 95% confidence interval (CI), 1.0-1.6]. It was as low as 0.4% (5/1338; 95% CI, 0.1-0.9) in term births with maternal HIV-1 RNA level at delivery below 50 copies/ml. MTCT increased with viral load, short duration of antiretroviral therapy, female gender and severe premature delivery: 6.6% before 33 weeks versus 1.2% at 37 weeks or more (P < 0.001). The type of antiretroviral therapy was not associated with transmission. Intrapartum therapy was associated with four-fold lower MTCT (P=0.04) in case of virological failure (> 10000 copies/ml). Elective cesarean section tended to be inversely associated with MTCT in the overall population, but not in mothers who delivered at term with viral load < 400 copies/ml [odds ratio (OR), 0.83; 95% CI, 0.29-2.39; P = 0.37]. Among them, only duration of antenatal therapy was associated with transmission (OR by week, 0.94; 95% CI, 0.900-0.99; P = 0.03). Conclusions: Low maternal plasma viral load is the key factor for preventing MTCT. Benefits in terms of MTCT reduction may be expected from early antiretroviral prophylaxis. The potential toxicity of prolonged antiretroviral use in pregnancy should be evaluated. (c) 2008 Wolters Kluwer Health vertical bar Lippincott Williams and Wilkins.

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CROI. **Update on HIV infection and breastfeeding: Overview of the CROI 2008, Boston.** 2008.

**Notes.** Several presentations addressing the relation of infant feeding and HIV postnatal transmission were presented at the CROI 2008 and could contribute to update the WHO PMTCT and infant feeding guidelines in the future.

#### **Postnatal HIV transmission, infant outcomes and infant feeding practices**

In a pooled analysis of individual data from South African and a West African cohort studies (abstract # 46), the overall risk of postnatal HIV infection was 3.9% (95% CI, 2.3-6.5) among children breastfed for <6Mo and 8.7% (95%CI, 6.8-11.0) among children breastfed for >6Mo (adjusted hazard ratio: 1.8 [0.9-3.4], p=0.06). It appears therefore that breastfeeding duration is also a major determinant of HIV transmission in addition to maternal immune status. The estimated risk of transmission was not different in exclusively and predominantly breastfed children. Exposure to breastfeeding mixed

with solids during the first 2 months increased the postnatal risk of acquisition of HIV (adjusted hazard ratio: 2.9 [1.1-8.0],  $p=0.04$ ).

In the Vertical Transmission Study, in South Africa (abstract # 636), the estimation of the 18-Month HIV-free survival according to infant feeding practices shows that breastfeeding of HIV-uninfected infants beyond 6 months of age increases the risk of HIV acquisition without gains for survival. It remains important to identify means of making breastfeeding safer for HIV-infected women who have no choice than to continue breastfeeding.

#### **Maternal outcomes and infant feeding practices**

In the ANRS Ditrane-Plus cohort study in Abidjan (abstract # 73), a study of the incidence of pregnancies according to infant feeding practices was conducted. Before 12 months post-partum, the risk of pregnancy was comparable in replacement feeding and breastfeeding groups: 4%. Between 12 and 24 months post-partum, the risk of pregnancy was significantly twice lower among replacement feeders than breast-feeders. Replacement feeding was not responsible of a greater incidence of pregnancies in this West African urban context. The incidence of pregnancies was controlled by the systematic offer and the frequent use of contraceptive services that should indeed accompany all alternatives to breastfeeding.

#### **Antiretrovirals in breastfeeding women**

The Kisumu Breastfeeding Study (abstract # 45LB) in Kenya was an interventional prospective cohort of children from lactating women on HAART to prevent MTCT. Overall transmission rates were 3.9% at 6-week, 5% at 6-month, 5.9% at 12-month, and 6.7% at 18-month. There was no difference in HIV transmission according to baseline maternal CD4 count. For those infant who became infected by the first 6-weeks of life, resistance was initially not detected (abstract # 84LB). However resistance emerged during the breastfeeding period.

In the MASHI trial in Botswana (abstract # 637), the MTCT rate at one month was 1.2% among breastfeeders and 1.1% among formula feeders. Breastfeeding was not a risk for MTCT within the first month of life of children exposed to maternal HAART and receiving also infant antiretroviral prophylaxis.

The preliminary Kesho Bora results (abstract # 638) from this trial conducted in 5 African sites were presented. The HIV transmission rate at 12-month was 7.6% in breastfed children of women treated by HAART with less than 200 CD4 count at baseline and 5.8% among women with more than 500 CD4 count at baseline and not receiving any ARV after delivery.

New results of the Dream cohort (abstract #369) in Mozambique were presented. In this prospective cohort of 341 mother-infant pairs followed from pregnancy until 12 months postpartum, mother breastfed on HAART until 6 months post delivery. HAART continued beyond 6 months in women who initiated HAART for their own health. The HIV MTCT rates were: 1.2% at birth, 1.9% at 6 months, and 2.8% at 12 months. The authors observed 4 late post-natal HIV-1 infections (> 1 month of age) only in this cohort.

The Breastfeeding, Antiretroviral and Nutrition (BAN) Study (abstract # 648) conducted in Malawi reported on the antiretroviral concentration in breastmilk. Although 3TC concentrations in breast milk were 2.6-fold higher than in maternal plasma, infant plasma exposure was minimal (1% of breast milk). NVP concentrations in breast milk were ~70% that of maternal plasma, with low exposure (20% of breast milk) in infants. NFV exposure in breast milk is minimal (8% of maternal plasma), with no drug found in infants. Infants' plasma concentrations for all antiretrovirals were well below concentrations required for treatment, suggesting minimal risk for drug toxicity. 3TC and NFV exposure in infants would suggest minimal risk for resistance in HIV-infected children; however, low-level NVP exposure via breast milk may predispose HIV-infected infants to resistance.

#### **Antiretrovirals in breastfed children**

The PEPI-Malawi Study (abstract # 42LB) evaluated in a randomized controlled trial if 14 weeks of extended daily infant antiretroviral prophylaxis with NVP (group 2,  $n=1016$ ) or NVP+ZDV (group 3,  $n=996$ ) with early weaning from age 4-6 months would reduce postnatal transmission of HIV compared to controls receiving a sdNVP and one week ZDV

(group 1, n=1003). At age 9-month, the risk of HIV infection was 10.6% in group 1, 5.2% in group 2 and 6.4% in group 3. However, at 18 months, HIV rate reached 13.9% in group 1, 10.1% in group 2 and 10.2% in group 3. Postnatal transmission occurred after NVP cessation among breastfed children. Post-exposure prophylaxis in breastfed children could reduce postnatal transmission but should probably be maintained over the entire breastfeeding duration.

In the SWEN randomized controlled Trial (abstract # 43) conducted in Ethiopia, India and Uganda, an extended infant post-exposure prophylaxis with daily NVP to 6 weeks in breastfed children of HIV-infected mothers was assessed to reduce postnatal HIV transmission. The 6-week HIV rate in the extended-NVP arm was 2.5% versus 5.3% in the sd-NVP arm ( $p=0.009$ ) but the 6-month HIV rate was 8.9% in the extended-NVP arm versus 6.9% in the sd-NVP arm ( $p=0.16$ ). The extended-NVP arm was safe but postnatal transmission occurred after stopping NVP in breastfed children with a reduction of long-term efficacy and occurrence of resistance to NNRTIs in infected children. .

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